**Title:** Infant T-Cell Acute Lymphoblastic Leukemia Presenting with Macrocephaly: A Case Report

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**Abbreviations:**

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| ALL | Acute lymphoblastic leukemia |
| AML | Acute myeloid leukemia |
| BESSI | Benign enlargement of the subarachnoid space of infancy |
| CNS | Central nervous system |
| COG | Children's Oncology Group |
| CSF | Cerebrospinal fluid |
| HSCT | Hematopoietic stem cell transplant |
| IT | Intrathecal |
| MLL | Mixed-lineage leukemia |
| MRD | Minimal residual disease |
| MRI | Magnetic resonance imaging |
| MUD | Matched unrelated donor |

***Abstract***

A 6.5-month-old girl presented to a pediatrician for a second opinion regarding worsening macrocephaly and developmental regression. She then underwent neurosurgical evaluation. Rapid-sequence magnetic resonance imaging was significant for benign enlargement of the subarachnoid space of infancy. A complete blood count was significant for 33% blasts in the peripheral blood. Flow cytometry of the peripheral blood established a diagnosis of T-cell Acute Lymphoblastic Leukemia (ALL). T-cell ALL has been rarely reported and our patient's presentation with macrocephaly is particularly unique.

***Introduction***

While acute lymphoblastic leukemia (ALL) is the most common childhood cancer, only 2-5% of patients have central nervous system (CNS) involvement at the time of diagnosis (5,6). Infant's less than a year of age comprise 2.5-5% of these patients (5,6). The mechanism of CNS positivity remains unknown, but is attributed to hematogenous extravasation of cancer cells and is more frequently seen in T-cell ALL compared to B-cell ALL (7,9). The vast majority of infant leukemias are either B-cell ALL or acute myeloid leukemia (AML). Mixed-lineage leukemia (MLL) gene rearrangement is also frequently seen in this population and confers a negative effect on prognosis (4,12). Little is known about infant T-cell ALL, given the rarity of the diagnosis. We describe a case that represents a unique presentation with macrocephaly as the initial presenting sign of infant T-cell ALL.

## Case Description

A 6.5-month-old girl, who was a product of in-vitro fertilization born full-term, presented to her pediatrician for macrocephaly. Her head circumference had drastically increased from the 59th percentile at 4-days of age to the 89th percentile at 4-months-old and was greater than the 99th percentile at 6-months of age, per the World Health Organization Girls Growth Chart for 0-2 Years of Age. Additionally, she had poor weight gain and chronic nasal congestion over the preceding few months. Her physical exam showed scattered, pink macular lesions over her scalp with a single, similar appearing lesion on her mons pubis along with scattered petechiae (Figure 1.). These lesions were thought to be atopic or vascular in nature and had been present for a month prior to presentation. She also had prominent parietal scalp veins. She previously met normal developmental milestones, but had recent regression and had stopped rolling over and had decreased head control.

Given these concerns she was sent to our institution for neurosurgical evaluation. Initial rapid-sequence magnetic resonance imaging (MRI) of her head showed benign enlargement of the subarachnoid space of infancy (BESSI). Due to her developmental regression, she then underwent a complete MRI and magnetic resonance angiography of her head which showed marrow expansion of the clivus and occiput. A complete blood count was notable for a white blood cell count of 17.0 cells/mm3, hemoglobin of 7.0 g/dL, and platelet count of 46.0 cells/mm3. Due to anemia and thrombocytopenia, hematology was consulted, and the differential eventually showed 33% blasts.

Flow cytometry of her peripheral blood was negative for B-cell antigens and positive for T-cell antigens CD3 and CD7. Additionally, the majority of the blasts lacked CD117 positivity, making a precursor phenotype unlikely. Myeloid markers, including CD11b, 13, 14, 15, 16, 33, and 64 and myeloperoxidase were negative. Cerebrospinal fluid (CSF) analysis was significant for two nucleated cells and the presence of blasts. Bone marrow biopsy showed 81% blasts and cytogenetic evaluation showed three related abnormal clones, trisomy 8, 11q13 to 11q23 deletion and material of unknown origin replacing Xq24 to Xqter. Altogether, this was consistent with a diagnosis of Infant T-cell ALL. Induction chemotherapy was started per Children's Oncology Group (COG) protocol AALL15P1, consisting of intrathecal (IT) methotrexate, IT and intravenous cytarabine, doxorubicin, PEG-asparaginase, prednisolone and vincristine.

Shortly after initiation of induction chemotherapy, the patient's skin lesions, which were consistent with leukemia cutis, began to resolve. Additionally, her head circumference decreased and her head control began to improve after completion of her induction chemotherapy. Her end-induction bone marrow analysis demonstrated 20% blasts and minimal residual disease (MRD) assessment by flow cytometry revealed 22.4% of the white blood cells to be a population of atypical T-cells with an immunophenotype similar to that identified at the time of diagnosis. Consolidation therapy was started with a regimen mirroring COG protocol AALL1231 with nelarabine added to the chemotherapy backbone. Following consolidation, there were 8% blasts in the bone marrow and MRD remained positive at 0.8%. Throughout treatment, the patient had multiple subdural

hematohygromas that required drainage and eventually underwent placement of a ventriculoperitoneal shunt.

Given the rarity of infant T-cell ALL, multiple opinions were sought from colleagues with specific expertise in T-cell ALL. Because the bone marrow was MRD positive following consolidation, it was recommended that the patient undergo an allogeneic hematopoietic stem cell transplant (HSCT) if and when MRD negativity could be achieved. She next received high dose cytarabine and asparaginase, after which she achieved MRD negativity. She successfully underwent a HSCT from a matched unrelated donor (MUD) after conditioning with cyclophosphamide and total body irradiation.

At the time of writing, the patient remains in remission. Her head circumference remains stable and she continues to have developmental delays for which she receives therapies.

## *Discussion*

Infant leukemia is a term that generally refers to ALL or AML that is diagnosed in children less than 1 year of age (7). In comparison to older children, children with infant leukemia more commonly have evidence of bulky or extramedullary disease, including hepatosplenomegaly, CNS involvement, and leukemia cutis, all of which were present in our patient at diagnosis (1,8). Infants with ALL fare worse than their older counterparts and a T-cell phenotype is rare in infants with ALL (3). In the Interfant-99 trial which

enrolled patients aged 0 to 12 months with a diagnosis of ALL, the 4-year event free survival was 47%, though these patients presented primarily with B-cell ALL (6,11,14). MLL rearrangements occur in about 5% of all childhood ALL cases, but in 80% of those with infant ALL (2,13). MLL rearrangements are associated with a particularly poor prognosis. The exact etiology of MLL rearrangements is unclear, though it has been hypothesized that they are acquired in utero (4). Infant ALL remains difficult to treat, with outcomes inferior to those of older children.

CNS involvement in children with ALL typically presents with leukemia cells in the CSF, and intracranial chloromas are quite rare (8). In review of the current literature, we noted one other case of infant T-cell ALL presenting with macrocephaly along with cytopenias in an 8-month-old male with increasing head circumference and developmental regression (10). He was reported to have hydrocephaly, brain atrophy, and ventricular enlargement on CT imaging (10). Conversely, our patient's MRI showed marrow expansion of the skull base and occiput consistent with leukemic involvement. Narrowing of the CSF outflow tract leading to macrocephaly was postulated but never assessed with venous specific imaging. This remains the primary hypothesis of our patient's macrocephaly as leukemic infiltrate in the marrow space of the skull could lead to obstruction of CSF outflow or poor reuptake of CSF due to hyperleukocytosis in the setting of infant T-cell ALL.

Macrocephaly in an infant requires close attention by the clinician, especially in the setting of neurologic changes and loss of developmental milestones. Though non-

specific, if accompanied by additional systemic signs including hepatosplenomegaly, fever, poor weight gain, and hematologic abnormalities, further evaluation is warranted to rule out a hematologic malignancy. Infant ALL is rarely of T-cell lineage, and in this case, lacked a characteristic infant MLL gene rearrangement. Our patient ultimately was able to achieve MRD negativity and successfully underwent a MUD HSCT. She remains in remission at this time, almost a year since her initial diagnosis, and continues to be followed closely.

**Author Disclosure:** The authors declare that there are no conflicts of interest regarding the publication of this article.

**Ethics Statement:** Proper consent was obtained for the use of the photos in Figure 1.

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**Figure 1**: Pink macular lesions over our patient's scalp (A) and mons pubis (B) along with scattered petechiae. These lesions were found to be consistent with leukemia cutis.